# ФУНКЦИОНАЛЬНЫЙ ГИПОПАРАТИРЕОЗ НА ФОНЕ ГИПОМАГНИЕМИИ ПРИ ДЛИТЕЛЬНОМ ПРИЕМЕ ИНГИБИТОРА ПРОТОННОЙ ПОМПЫ

© Л.В. Егшатян[1,2]

[1]ФГБОУ ВО «Московский государственный медико-стоматологический университет имени А.И. Евдокимова», Москва, Россия
[2]ФГБУ «Национальный медицинский исследовательский центр эндокринологии» Минздрава России, Москва, Россия

Гастроэзофагельная рефлюксная болезнь (ГЭРБ) – воспалительное поражение дистальной части пищевода вследствие повторяющегося заброса в пищевод желудочного и (или) дуоденального содержимого. В настоящее время наблюдается тенденция к увеличению заболеваемости ГЭРБ в мире, особенно в развивающихся странах. Лечение ГЭРБ включает рекомендации по изменению образа жизни пациента и медикаментозную терапию – первоначально ингибиторов протонной помпы (ИПП). Длительное применение ИПП связано с различными осложнениями, такими как дефицит железа, гипомагниемия, гипокальциемия, гипокалиемия, остеопороз и переломы костей, хронические заболевания почек, острая почечная недостаточность, пневмония и так далее. В литературе все чаще появляются описания клинических случаев развития гипомагниемии. В феврале 2011 г. управление по санитарному надзору за качеством пищевых продуктов и медикаментов FDA (Food and Drug Administration) опубликовало сообщение о новом нежелательном явлении при длительном приеме ИПП – гипомагниемии. В статье представлен результат собственного наблюдения 56-летнего пациента, обратившегося за консультацией с жалобами на судороги, тремор, боли в мышцах, нарушение ритма сердечной деятельности, общую слабость, вызванные гипомагниемией, гипокальциемией и гипокалиемией при низком уровне паратиреоидного гормона на фоне длительного применения ИПП по поводу ГЭРБ. На фоне отмены ИПП и назначения препаратов магния отмечено улучшение состояния, восстановление электролитных нарушений и функции околощитовидных желез. Причинно-следственная связь электролитных нарушений с ИПП подтверждена при повторном назначении ИПП и возобновлении гипомагниемии.

КЛЮЧЕВЫЕ СЛОВА: клинический случай; гастроэзофагельная рефлюксная болезнь; гипопаратиреоз; паратиреоидный гормон; гипомагниемия; ингибиторы протонной помпы; гипокалиемия

# FUNCTIONAL HYPOPARATHYROIDISM SECONDARY TO MAGNESIUM DEFICIENCY IN LONG-TERM USERS OF PROTON PUMP INHIBITOR

© Lilit V. Egshatyan[1,2]

[1]Moscow State University of Medicine and Dentistry named after A.I. Evdokimov, Moscow, Russia
[2]Endocrinology Research Centre, Moscow, Russia

Gastroesophageal reflux disease (GERD) is a gastrointestinal motility disorder that results from the reflux of stomach contents into the esophagus resulting in symptoms or complications. GERD is now widely prevalent around the world, with clear evidence of increasing prevalence in many developing countries. Treatment for most people with GERD includes lifestyle changes and medication. Proton pump inhibitors (PPIs) are a mainstay therapy for all gastric acid-related diseases. Long-term use of PPIs is associated with hypomagnesaemia, hypokalemia, hypocalcaemia, osteoporosis and bone fractures, chronic renal disease, acute renal disease, and other. Clinical concerns arise from a small but growing number of case reports presenting PPI-induced hypomagnesaemia. In 2011 the U.S. Food and Drug Administration is informing the public that prescription PPI may cause low serum magnesium levels if taken for prolonged periods of time.

In this article, we present the case of a 56-year-old patient with muscle cramps, violation of cardiac rhythm, lethargy and other caused by hypomagnesaemia, hypocalcaemia and hypokalemia with a low parathyroid hormone level while using a PPI. After magnesium repletion abnormalities resolved. A causal relation with PPI use was supported by the recurrence of hypomagnesaemia after re-challenge.

KEYWORDS: case report; gastroesophageal reflux disease; hypoparathyroidism; parathyroid hormone; hypomagnesaemia; proton pump inhibitor; hypokalemia

## BACKGROUND

Gastroesophageal reflux disease (GERD) is a condition, characterized by indicative symptoms and/or inflammation of distal esophagus due to return of the stomach and/or duodenal contents into the esophagus [1]. 6-th European gastroenterology week's manifest "20th century is a century of peptic ulcer disease, 21th – a century of GERD" reflected the growing incidence of GERD [2]. Retrospective analysis of initial esophagogastroduodenoscopy (EGD) reports on 5107 patients with gastroenterologic complaints in 5-year

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period showed, that endoscopic features of reflux-esophagitis were found in 27,8%, catarrhal esophagitis in 17,4% and erosive esophagitis in 10,4% of patients [2].

Known causes of GERD are weakening of lower esophageal sphincter, inability of the mucosa to withstand the damaging action of the stomach contents, gastric emptying distorders, etc. GERD treatment includes lifestyle modifications and medications. Primary medications are proton-pump inhibitors (PPIs), which block H+/K+-ATPase of gastric parietal cells. Ca2+/Mg2+-sensitive receptor plays essential role in hydrochloric asid and gastrine (G-cells) secretion, and this mechanism acts through activation of H+/K+-ATPase [3].

As any other medication, PPIs have various side effects, which are not very prevalent, however, when treatment is longitudinal, their prevalence can increase. Most of potential side effects are relative to direct action of PPIs on parietal cells. It is known that long-term (more than one year) treatment with PPIs is associated with increased risk of lowered absorption of ferrum, calcium, magnesium, vitamin B12, as well as increased risk of pneumonia, gastrointestinal infections, osteoporosis and fractures, neoplasm development, interstitial nephritis, etc. [4-7]. There is emerging data on clinical cases of significant hypomagnesemia in patients on long-term PPIs treatment and the mechanism of this side effect is unclear. Supposedly, PPIs are linked with other risk factors for hypomagnesemia, concerning its high prevalence (10-80%). The risk of hypomagnesemia in general population is approximately 2%, 10-20% in hospitalized patients, 50-60% in patients of intensive care departments, 50-60% in chronic alcoholics, up to 25% in diabetic patients [8, 9]. Hypomagnesemia is highly prevalent in patients with type 2 diabetes mellitus (T2DM) [10]. In these patients, the considered cause is an increase of urinary magnesium excretion due to glycosuria, decrease in intestinal magnesium absorption and redistribution of magnesium from the circulation into the cells caused by intracellular magnesium deficiency induced by insulin deficiency [11, 12].

Hypomagnesemia associated with the use of PPIs was firstly described in 2006 [13]. In February 2011, FDA published an announcement concerning new adverse event of prolonged PPIs treatment – hypomagnesemia [14]. In many patients with hypomagnesemia, inadequately normal or lowered parathyroid hormone (PTH) is observed, resulted from inhibition of its secretion or synthesis. Additionally, these patients may develop PTH resistance with vitamin D deficiency and hypocalcemia [15-20].

## DESCRIPTION OF THE CASE

Patient B, 57 y.o., visited an outpatient department in September 2017.

**Presenting complaints**. On the first visit, the patient presented with following complaints: fatigue, edginess, decreased alertness, syncopes, muscle pain and cramps, tremor, dry mouth, heart palpitations.

**Anamnesis**. Patient had no family history on endocrine disorders. In 2005, he was diagnosed with GERD and treatment with omeprazole (20-40 mg daily) was initiated. In March 2016, his condition worsened: he had complains on acute pain in the larynx, acid and air burps, epigastric pain and compression feeling after eating. Without consulting a doctor, the patient increased the dosage of omeprazole to 60 mg daily, which he was taking for 3 months and then decreased to 40 mg daily.

In December 2016, he had an appointment with a cardiologist with complaints on increased blood pressure (up to 160/90 mm Hg), heart palpitations, leg cramps, and fatigue. Electrocardiography (ECG): sinus rhythm, heat rate 100-86/minute, tachycardia with elements of atrial rhythm migration, horizontal axis, hypertrophy and overload of left ventricle, electrometabolic myocardial changes. Cardiologist initiated antihypertensive therapy with ACE inhibitor and beta-blocker. Laboratory investigation revealed hypocalcemia (1,98 mmol/L (reference range 2.15-2.55)) and hyperglycemia (7,3 mmol/L (reference range 3.1-6.1), the patient was referred to see endocrinologist. Patient reported that in 2015 he had normoglycemia. As the patient also had elevated HbA1c level (7.8%), he was diagnosed with T2DM, endocrinologist initiated treatment with metformin 2000 mg daily and gave dietary recommendations; to compensate hypocalcemia, patient was also prescribed a calcium carbonate 2000 mg + colecalciferol 400 IU daily. As there was no clinical effect, the patient stopped taking calcium+vitamin D medication in February 2017.

As patient's condition worsened, he started having more severe muscle cramps and lowered alertness, and the patient referred to a neurologist. Electroencephalography revealed episodes of high-amplitude, low-wave activity. Laboratory tests revealed severe hypocalcemia (1,67 mmol/L (2,15-2,55)), hypokalemia and hyperglycemia. The patient was referred to endocrinologist for a second time.

His first visit to our department was on 4 September 2017. Initial laboratory results are presented in table 1.

**Diagnostic assessment**. On physical examination patient had positive Trousseau (spasm of the hand muscles after a blood pressure cuff is placed around the arm, inflated and held in place for 3 minutes) and Chvostek (contraction of facial muscles after the facial nerve is tapped in front of tragus) signs. Blood pressure 143/85 mm HG, pulse 102/min, BMI 26,2 kg/m2.

ECG – paroxysmal supraventricular tachycardia, QT interval prolongation, left ventricle hypertrophy, electrometabolic myocardial changes.

As the patient had hypocalcemia and lowered PTH, we diagnosed hypoparathyroidism.

- Hypomagnesemia and hypokalemia are not characterisitic features of main forms of hypoparathyroidism (autoimmune, idiopathic, or as a component of genetic disorders). Hypomagnesemia is often accompanied not only by hypocalcemia, but also by hypokalemia and hyperkaliuria that can lead to metabolic alkalosis in severe cases [21, 22]. If a patient has hypomagnesemia and hypocalcemia, first treatment step is the correction of magnesium deficiency.

**Interventions**. We discontinued omeprazole and initiated parenteral magnesium treatment: intramuscular magnesium sulfate 5,0 g (20 ml of 25% solution), continued

**Table 1.** Initial laboratory results

| Measurement | Value | Reference range |
|---|---|---|
| Calcium, mmol/L | 1,82 | 2,15-2,55 |
| Phoshorus , mmol/L | 1,39 | 0,87-1,45 |
| Albumin, g/L | 40,5 | 35-52 |
| Magnesium, mmol/L | 0,31 | 0,66–1,07 |
| Potassium, mmol/L | 3,2 | 3,5-5,1 |
| Sodium, mmol/L | 143 | 136 – 145 |
| Glucose, mmol/L | 6,7 | 4,1 - 5,9 |
| $HbA_{1c}$, % | 7,1 | |
| Cholesterol, mmol/L | 5,48 | < 5,18 |
| Creatinine, μmol/L | 98 | 64-111 |
| GFR, CKD-EPI, ml/min/1,73m$^2$ | 86 | |
| Urea, mmol/L | 6,3 | 2,1-7,1 |
| PTH, pmol/L | 0,7 | 1,6-6,9 |
| 25(OH)D, ug/mL | <4 | 30-100 |
| blood pH | 7,39 | 7,32-7,42 |
| Urine Albumin/creatinine, mg/g | 19 | < 30 |

with drop infusion of 4,0 g magnesium sulfate in 200 ml 0,9% sodium solution for every 4 hours. After 1-2 hours after initiated treatment, the patient reported that tremor and tachycardia ameliorated. Trousseau and Chvostek signs also showed abatement. ECG reveal improvement of tachycardia and normalization of QT duration.

**On the next day** of treatment, the patient reported further condition improvement: abatement of cramps, tremor and tachycardia. Normalization of both magnesium (0.67 mmol/L) and PTH (4.3 pmol/L) levels suggested that this was not the case of chronic hypoparathyroidism. We also observed a slight increase in calcium level (1.91 mmol/L).

- With magnesium deficiency replenishment, calcium level normalization is more delayed, compared to PTH.

We continued parenteral magnesium sulfate treatment, injections of 4-8 ml 25% (1-2 g) solution every 6 hours for 3 days, then switched on oral treatment. Changes in laboratory results are shown on figure 1.

As patient also had vitamin D deficiency, despite of normal magnesium levels he still had mild hypocalcemia (2,13 mmol/L) and PTH reached upper normal values (fig. 1). To correct the deficit and prevent secondary hyperparathyroidism development, we initiated colecalciferol treatment, 50.000 IU weekly.

We observed that glycemia tended to decrease (without T2DM treatment correction), and potassium level normalized (fig. 1).

**After 1 month of treatment** with magnesium and colecalciferol, patient had no complaints. Trousseau and Chvostek signs were negative. Lab results showed normalization of all parameters: PTH 6,0 pmol/L, calcium 2,17 mmol/L, magnesium 1,01 mmol/L, potassium 4,2 mmol/L, sodium 142 mmol/L, glucose 5,6 mmol/L.

**To comfirm the relation between omeprazole and development of hypomagnesemia**, we reinitiated omeprazole treatment 40 mg daily, without discontinuing magnesium therapy, for 1 week. After the week, magnesium level decreased to 0,69 mmol/L. We recommended the patient to take omeprazole in minimally effective dose only under strict observation of gastroenterologist and blood magnesium level monitoring.

## DISCUSSION

The main causes of hypomagnesemia are loop and thiazide diuretics, aminoglycosides, immunosuppressants (tacrolimus, cyclosporine, rapamycin) and chronic alcoholism, excessive sweating, malnutrition, diabetes mellitus, hyperthyroidism, malabsorption, etc. Among these causes, our patient only had T2DM, which could influence magnesium level [11, 12]. However, in a study, which included more than 127 thousand people with no T2DM, authors found strong inverse correlation between magnesium intake and T2DM development

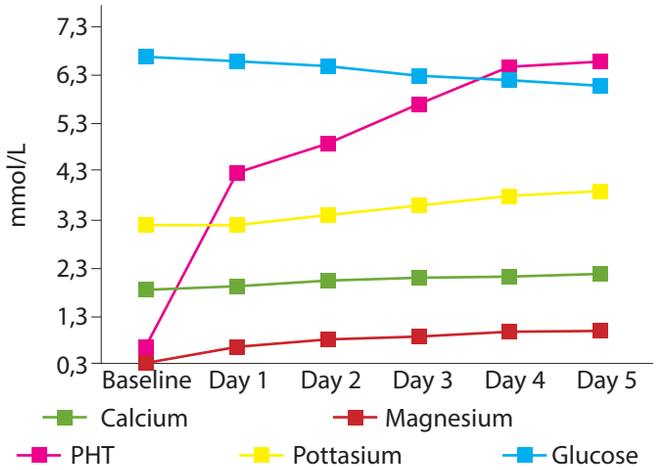


**Fig. 1.** Changes in lab results during magnesium medications treatment during the first five days

risk. Through the observation period (18 years), 4,3% developed T2DM. [23]. Our patient had no family history of T2DM, and the diagnosis was set in 2016. On one hand, T2DM could be a complication of hypomagnesemia in this patient, on the other – T2DM could deteriorate it. After compensation of magnesium deficit, patient tended to have normoglycemia without adjusting the metformin dose, which supports the first suggestion. Therefore, taking in account patient's history, only long-term use of omeprazole (occasional use for 12 years, constant use of high doses for a year) could be the cause of hypomagnesemia. This suggestion was proved by recurrence of hypomagnesemia after reinitiation of omeprazole treatment.

To date, the mechanism of hypomagnesemia on the background of PPIs in unclear. Considered mechanism is related to change of intestinal pH induced by PPIs, which possibly affect intestinal transient receptor protein channels, TRPM-6 and TRPM-7 [24].

Most of the patients with hypomagnesemia have no clinical presentation. Clinical features of mild hypomagnesemia are fatigue, tiredness, irritability, depression, apathy, hypomnesia, dizziness, etc. Hypomagnesemia has clinical presentation in cases of blood magnesium level less than 0,5 mmol/L. Neuromuscular disorder caused by hypomagnesemia was described in 1932 [25]. Symptom intensity also depends on concomitant blood calcium and potassium decrease. In our patient, severe hypomagnesemia was accompanied by hypocalcemia and hypocalemia, thus determining the clinical manifestation.

Adequate magnesium supplementation contributes to vitamin D depot maintenance, calcium homeostasis [26] and function of parathyroid glands. Physiologic fluctuations in magnesium concentration does not affect parathyroid function, however, moderate alteration deteriorate PTH secretion. Inadequately normal or lowered PTH is seen in many patients with hypomagnesemia [17]. This could be explained by the fact that severe chronic hypomagnesemia is a marker for general magnesium deficit. Magnesium deficiency alters secretory mechanisms and tissue sensibility for PTH, affecting the function of phosphatidylinositol system and/or decreasing adenylatecyclase activity in parathyroid glands and in target tissues, as both of these mechanisms are magnesium-dependent. It was also shown that compared to PTH secretion alteration, greater degree of magnesium deficit is required to induce target tissues resistance [27-30]. When bone and kidney tissues are resistant to PTH, hypocalcemia occurs as the result of lack in 1α-hydroxilation of vitamin D, mediated by PTH, which leads to vitamin D deficiency and decrease of bone resorption [20].

In this patient we revealed magnesium-dependent PTH suppression with development of transient hypoparathyroidism and hypocalcemia. Hypoparathyroidism transience and relation with hypomagnesemia was confirmed after normalization of blood magnesium level. It is possible that vitamin D deficiency was also a result of hypomagnesemia and functional hypoparathyroidism, however, taking in account that vitamin D deficiency is a wide-spread condition, it is impossible to establish their relation.

Intracellular magnesium deficit leads to decrease of adenosine triphosphate activity, which causes the increase of potassium channels quantity and activity [21]. Magnesium deficit also causes the increase in potassium channel activity in limb cells [22]. As a result, hypokalemia is resistant to potassium infusions and supplementations and can be treated only by correcting magnesium deficit. In our patien we did not use potassium medications, potassium level normalized after treatment with magnesium medications and compensation of hypomagnesemia.

Relation between electrolyte disorders and omeprazole treatment was proved in this patient by the fact of recurrence of hypomagnesemia after reinitiation of PPIs treatment, despite of continued magnesium supplementation.

## CONCLUSION

Our clinical case highlights the importance of magnesium in human body, which is absorbed from food, water and salt. If intestinal magnesium absorption decreases, for example, in cases of long-term PPIs treatment, various electrolyte disorders can be observed (hypocalcemia, hypokalemia, hyperglycemia), which are associated with magnesium deficit. This side effect is not frequent, but its frequency may increase with long-term PPIs treatment, which was demonstrated in our patient. PPIs, as well as any other drug, should only be prescribed for therapeutic indications from corresponding clinical recommendations and product instructions.

## ADDITIONAL INFORMATION

**Conflict of interests**. Author declares no explicit and potential conflicts of interests associated with the publication of this article.

**The patient's informed consent**. The patient provided his informed consent for the publication of this case report in "Osteoporosis and Bone Diseases" journal.

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**ИНФОРМАЦИЯ ОБ АВТОРАХ [AUTHORS INFO]**

**Егшатян Лилит Ваниковна**, к.м.н. [**Lilit V. Egshatyan**, MD, PhD] адрес: Россия, 127473, Москва, ул. Делегатская 20, стр. 1 [address: 20\1 Delegatskaya ul., 127473, Moscow, Russia]; адрес: Россия, 117036, Москва, улица Дм.Ульянова, д.11. [address: 11 Dm.Ulyanova street, 117036 Moscow, Russia]; ORCID: http://orcid.org/0000-0001-8817-1901 eLibrary SPIN: 4552-5340; e-mail: lilit.egshatyan@yandex.ru

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